REMARKS

Telephonic Interview

A telephonic interview between Examiner Yaen and Mary Ann Brow was conducted on October 25, 2006. The discussion related to pending claims 35-39 and to the 103(a) rejections in the Office Action mailed on July 12, 2006, which are summarized below. No agreement was reached regarding the rejections. Applicant thanks Examiner Yaen for taking the time to discuss this matter.

Rejections

Claims 35-39 are pending in the present application. These claims stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cleary, *et al.* (Cell, 1986, Vol. 44, pp97-106) ("Cleary") in view of Levy, *et al.*, Journal of Experimental Medicine, 1988, Vol 168 pp475-489) ("Levy") and Embleton, *et al.*, Nucle. Acids. Res., 1992, Vol 20, pp3831-3837) ("Embleton").

Prima facie obviousness requires: 1) a suggestion or motivation in the references or the knowledge generally available to combine or modify the reference teachings; 2) a reasonable expectation of success should the suggested combination or modification take place; and 3) a teaching or suggestion of all the limitations of the claims. A showing of obviousness will fail if any one of these elements is not met. See, *e.g.*, MPEP § 2143. Applicant submits that the combination of the Cleary, Levy and Embleton references fails on all three elements.

The Examiner admits that Cleary does not teach a multivalent idiotypic composition comprising V_H sequences that comprising more than one idiotype, or V_L regions comprising more than one idiotype (Office Action page 4). Levy is provided as corroborating Cleary. (Office Action page 3-4). Levy does not teach or suggest the multivalent compositions of the present invention.

The Examiner asserts that it would have been obvious to combine the Cleary and Levy references with the teachings of Embleton regarding improvements in the PCR cloning of immunoglobulin genes from B-lymphocytes which preserves the natural pairing of heavy chain and light chain and avoids the problem of screening artificial combinations. (Office Action page

5). Applicant respectfully disagrees for the following reasons:

I. The combination of references fails to teach each and every element of the instantly claimed method;

II. The references teach away from making such a combination; and

III. There would be no expectation of success in making the combination.

I. The references fail to teach each and every element of the instant claims.

Claim 35 recites, among other things, the following elements:

a. a plurality of V_L regions that are inserted into a first expression vector;

b. a plurality of V_H regions that are inserted into a second expression vector;

c. that the pluralities of said first and second expression vectors are co-transformed into a T-lymphoid cell, along with an amplification vector having a specific composition;

d. that the transformed cell is exposed to a particular aqueous solution, so as to identify a particular transformed cell;

e. that the particular transformed cell identified in (d) has the features of:

i. being capable of growth in the aqueous liquid of (d);

ii. expressing a mixture of V_L and V_H regions that necessarily are derived from at different tumor cells, as indicated by the recited combinations of different idiotopes.

The same elements are necessarily included in each of dependent claims 36-39. The references cited by the Examiner, whether taken alone or in any combination, do not teach any of elements (a)-(e), listed above. As such, this combination of references fails to teach each and every element of the claimed invention, and Applicant submits that the combination of Cleary, Levy, and Embleton thus does not establish obviousness of the instant claims, and respectfully requests that these rejections be removed.

II. The References Teach Away From the Combination.

Embleton teaches *away* from the combination with Cleary and Levy to make the compositions produced by the method of the present invention. Embleton teaches methods of preserving the natural pairings of V_H and V_L regions, specifically by amplifying immunoglobulin genes from within single cells, so as to avoid mixtures comprising the DNA of mixed populations of cells. See, *e.g.*, Abstract and second column on page 3831. Embleton also teaches the linking of the amplified V_H and V_L regions in a single molecule (*e.g.*, as shown in Fig. 1).

In contrast to Embleton, the method of the instant claims is not directed at preserving natural pairings of V_H and V_L regions. Rather, the instantly claimed method is directed at making a multivalent composition by *combining* the nucleic acid isolated from a mixed population of cells. See, *e.g.*, step (b) of Claim 35. Furthermore, the instant invention teaches that the amplified V_H and V_L regions from a single cell are not linked. Rather, the V_H regions of multiple tumor cells are cloned into a first expression vector and the V_L regions of multiple tumor cells are cloned into a second expression vector. The goals and outcomes of the two methods are thus diametrically opposed.

Furthermore, the instantly claimed method is directed at making the multivalent compositions of the invention in an individual transformed T-lymphoid cell that co-expresses variable regions derived from different cells. It is well established that individual B-cells express only a single V_H allele and a single V_L allele. Thus, co-expression of at least two V_H regions that differ by at least one idiotope necessarily requires co-expression of V_H regions derived from *different* tumor cells. The same applies to co-expression of V_L regions that differ by at least one idiotope. Embleton provides no teaching whatsoever that suggests DNA from different tumor cells should be co-expressed within a single transformed cell. In fact, co-expressing the mixture of variable regions recited in the instant claims is directly contrary to the teachings of Embleton.

Given that the entire purpose of the Embleton method is contrary to the objective of the method steps recited in the instant claims, one of skill in the art would hardly be motivated to use the teachings of Embleton for the purpose of creating the compositions produced by the methods of the present invention. Applicant submits that Embleton teaches away from the combination with Cleary and Levy, and the combination thus does not establish obviousness of the instant

claims and respectfully requests that these rejections be removed.

III) There would be no expectation of success

Because application of the method of Embleton to the cells of Cleary and Levy would not produce the multivalent composition produced by the method of the instant claims, one of skill in the art would have no expectation of success in adapting the method of Embleton to create the claimed method of making multivalent compositions. The method of Embleton is taught as a method of avoiding co-expressing variable regions derived from different cells. In contrast, the method of the present invention requires co-expressed variable regions derived from different cells. Furthermore, the method of the present invention recites that V_H regions are cloned into one expression vector and V_L regions are cloned into a separate, second expression vector. This is not compatible with the teaching of Embleton, in which the V_H and V_L regions recombined during PCR *to be part of a single molecule* (see, *e.g.*, Fig. 1 of Embleton). Thus, one of skill would not expect that use of the method of Embleton for making *single* molecules containing the V_H and V_L regions from *single* tumor cells, even if applied to the somatic mutants of Cleary and Levy, to be useful in producing the instantly claimed invention comprising *multiple, separate* molecules (expression vectors) containing the V_H and V_L regions from *multiple, different* tumor cells.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all reasons for rejection have been addressed and that Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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